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Wei Jian [US/US]; 23 Elizabeth Lane, Irvine, CA 92602 (US). TAM, Robert [BR/US]; 63 Wellington, Irvine, CA 92618 (US). RANEY, Anneke, K. [US/US]; 2268 Bliss Circle, Oceanside, CA 92056 (US).

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(74) Agent: **HANSBURG, Daniel**; Brown Raysman Millstein Felder & Steiner LLP, 900 Third Avenue, New York, NY 10022 (US).

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(71) Applicant (for all designated States except US): **RIB-APHARM, INC.** [US/US]; 3300 Hyland Avenue, Costa Mesa, California (US).

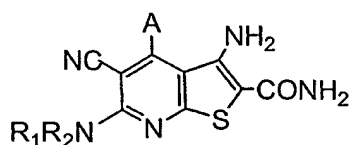
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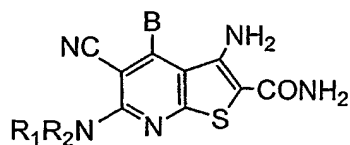
(75) Inventors/Applicants (for US only): **CHEN, Huanming** [CN/US]; 12 Amargosa, Irvine, CA 92602 (US). **ZHANG,**

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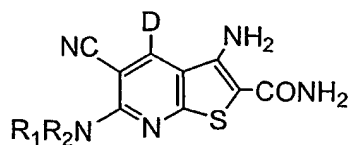
(54) Title: NOVEL HETEROCYCLIC COMPOUNDS AS IKK2 INHIBITORS WITH ANTI-HBV ACTIVITY



(I)a



(I)b



(I)c

(57) Abstract: This application relates to novel thienopyridines of Formula (I), which are IKK inhibitors and are useful for treating Hepatitis B infection and other diseases. This application also relates to pharmaceutical compositions comprising thienopyridines and the use of such compositions to treat Hepatitis B and other diseases.

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NOVEL HETEROCYCLIC COMPOUNDS AS IKK2 INHIBITORS WITH ANTI-HBV ACTIVITY

CROSS REFERENCE TO RELATED APPLICATIONS

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The present application claims benefit of U.S. Provisional Application Ser. Nos. 60/529,160, December 12, 2003.

BACKGROUND OF THE INVENTION

(1) IKK2 inhibitors

10 Nuclear factor- κ B (NF- κ B) is a ubiquitously expressed transcription factor that is essential to the regulation of such cellular functions as apoptosis, proliferation, and differentiation [Ghosh et al., *Annu Rev Immunol* 16:225, 1998]. NF- κ B accomplishes this regulation by coordinating the expression of genes responsible for protecting an organism after physical, chemical, and/or microbial damage. Thus, NF- κ B has an inherent role in the
15 induction of an immune response and concomitant inflammation. [Baeuerle and Baltimore. *Cell* 87:13, 1996]. The role of the NF- κ B pathway in an antiviral immune response is complex and its activity can be modulated by viral proteins (Bose et al., *PNAS* 100, 2003; Purcell et al., *Am J Physiol Gastrointest Liver Physiol* 280, 2001) as well as by other stimuli in interferon-dependent or independent manners (Pfeffer et al., *J. Biol. Chem.* 279:30, 31304-
20 31311, 2004).

The NF- κ B family of transcription factors includes a set of structurally related and evolutionarily conserved DNA binding proteins [Baldwin. *Annu. Rev. Immunol.* 14:649, 1996]. NF- κ B contains a nuclear localization sequence (NLS) that directs the protein to the nucleus to carry out its role in genetic regulation. However, under normal conditions NF- κ B
25 is sequestered in the cytoplasm because the NLS is masked by tightly bound inhibitory proteins known as Inhibitors of NF- κ B, or I κ B [Beg and Baldwin. *Genes Dev.* 7:2064, 1993; Thompson et al., *Cell* 80:573, 1995; Whiteside et al., *EMBO J.* 16:1413, 1997]. Signals known to activate NF- κ B do so by inactivating I κ B via phosphorylation, ubiquitination, and degradation. Thus, the elimination of I κ B exposes the NLS allowing NF- κ B to translocate to
30 the nucleus to activate specific target genes.

The signal responsible for inactivation of I κ B is typically a cellular response to an extracellular stimulus (Tumor Necrosis Factor α (TNF α), Interleukin-1 β (IL-1 β), lipopolysaccharide (LPS)) or to chemical and physical stress. The signal initiates from a cell surface receptor, such as the TNF-receptor or IL-1 receptor, and is internalized and transduced through the cell as a cascade of phosphorylation events. Each receptor binds unique adapter molecules specific to the receptor and stimulus and in turn activates downstream kinases including NF- κ B interacting kinase (NIK), MAPK/extracellular signal-regulated kinase kinase-1 (MEKK-1), and I κ B kinases α and β (IKK α/β). IKK β is responsible for liberating NF- κ B by phosphorylating the inhibitory subunit I κ B α . Phosphorylation of I κ B α by IKK β triggers ubiquitin ligase (Skp1/Cul 1/F-box protein FWD1) to ubiquitinate I κ B α and target it for degradation via the 26S proteasome [Yaron et al., *Nature* 396:590, 1998; Winston et al., *Genes Dev.* 13:270, 1999; Spencer et al., *Genes Dev.* 13:284, 1999].

I κ B kinases (IKK α and IKK β) are serine-threonine protein kinases and members of a large multiprotein complex known as the signalsome [Mercurio et al., *Science* 278:860, 1997; Woronicz et al., *Science* 278:866, 1997; Zandi et al., 91:243, 1997]. The signalsome is the machinery responsible for transducing the stimulus that results in NF- κ B activation. The genes encoding signalsome components have been cloned, expressed and reconstituted in vitro to demonstrate activation of NF- κ B via I κ B phosphorylation [Régnier et al., *Cell* 90:373, 1997; DiDonato et al., *Nature* 388:548, 1997; Zandi et al., *Cell* 91:243, 1997; Woronicz et al., *Science* 278: 866, 1997; Mercurio et al., *Science* 278:860, 1997; Cohen et al., *Nature* 395:292, 1998]. IKK family members share homologous amino-terminal kinase domains that are activated by NIK. In turn, IKK specifically phosphorylates I κ B α and I κ B β on regulatory serine residues. Genetic studies with IKK knock-out mice point to an essential role for IKK β in transmission of inflammatory signals, whereas IKK α is involved in developmental processes requiring NF- κ B activation [Takeda et al., *Science* 284:313, 1999; Hu et al., *Science* 284:316, 1999; Li et al., *Science* 284:321, 1999]. Embryonic fibroblasts isolated from IKK β -deficient mice show defects in TNF α - and IL-1-induced degradation of I κ B. Furthermore, inhibition of pro-inflammatory cytokine-induced I κ B degradation is not observed in cells derived from IKK α -deficient mice, suggesting that IKK β controls the NF- κ B activation rather than IKK α [Takeda et al., *Science* 284:313, 1999]. Moreover, a

catalytically inactive mutant of IKK β has been shown to inhibit inflammation via activation of NF- κ B through TNF α , IL-1 β , LPS, and anti-CD3/anti-CD28 stimulation [O'Connell et al., *J. Biol. Chem.* 273:30410, 1998; Woronicz et al., *Science* 278:866, 1997; Zandi et al., *Cell* 91:243, 1997.]. Thus, IKK β is considered by the inventors to be a validated target for
5 therapeutic interference in a variety of pathological situations, including chronic inflammatory and autoimmune diseases, viral infection, and cancer.

Some inhibitors of IKK β have been reported. WO 03/103661, WO 01/58890, and WO 03/037886 describe substituted thienopyridines and heteroaromatic carboxamide derivatives as inhibitors of IKK β . WO 01/68648 describes substituted β -carboline having IKK β
10 inhibiting activity. Substituted indoles having IKK β inhibitory activity are reported in WO 01/30774. WO 01/00610 describes substituted benzimidazoles with NK- κ B inhibitory activity. Additionally, aspirin and other salicylates have been reported to bind to and inhibit IKK β (M. Yin et al., *Nature*, 1998, 396, 77)

15 Substituted thienopyridines that inhibit cell adhesion are reported in US 2001/0020030 and in A.O. Stewart et al., *J. Med. Chem.*, 2001, 44, 988. Thienopyridines exhibiting gonadotropin releasing hormone antagonizing activity are reported in US 6313301. Substituted thienopyridines described as telomerase inhibitors are disclosed in US 5656638

(2) Anti-HBV agents

20 Despite various treatment options available for patients infected with Hepatitis B virus (hereafter "HBV"), sustained treatment success as evidenced by decrease of HBV DNA in serum and anti-HBe or HBs seroconversion is frequently limited to a relatively small patient population.

For example, interferon alpha has been widely used for the treatment of chronic HBV
25 infection for a number of years. However, interferon is effective only in certain subpopulations of chronic hepatitis B patients and is poorly tolerated. In other cases, lamivudine (3'-thia-2',3'-dideoxycytidine), a particularly strong inhibitor of HBV replication, is used to treat HBV infection. However, resistance against this nucleoside analog is increasingly common, and has limited its efficacy in a high proportion of patients. The most
30 recently approved treatment for HBV is adefovir dipivoxil (9-(2-((

bis((pivaloyloxy)methoxy)phosphinyl)methoxy)ethyl)adenine), and while this nucleoside analog is active against the lamivudine-resistant viruses, the sustained viral response rate is below 20%, and nephrotoxicity typically limits the maximum tolerated dose and/or treatment duration.

5 More recent developments in HBV research have led to clinical trials for several compounds with promising antiviral activity. For example, certain nucleoside analogs have been reported to exhibit significant anti-HBV activity (*e.g.*, 2'-fluoro-5-methyl-beta-L-arabinofuranosyluracil (Bukwang) and 2'-deoxy-5-fluoro-3'-thiacytidine (Gilead); 2'-deoxy-L-thymidine and 2'-deoxy-L-cytidine (both Idenix)). Similarly, carbocyclic nucleoside analogs
10 (6H-purin-6-one, 2-amino-1,9-dihydro-9-((1S,3R,4S)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl) monohydrate (Bristol-Myers Squibb), as well as acyclic nucleoside analogs with liver targeting properties (Remofovir; Ribapharm), were reported as having anti-HBV activity in clinical trials.).

However, while most of the recently discovered drugs with anti-HBV activity exhibited
15 promising *in vitro* antiviral activity, low response rates and the emergence of resistance limit the efficacy of these clinical candidates. Therefore, although various compositions and methods for HBV treatment are known in the art, there is still a need to provide new and/or improved compositions and methods for treatment of HBV infections in human patients.

Thus, in light of the limited efficacy, resistance profiles, and toxicity of current anti-
20 HBV drugs, there is a strong need for novel anti-HBV drugs that are more effective and less toxic and that exhibit a different resistance profile.

Therefore, it is an object of the present invention to provide a compounds and methods for the treatment of HBV infection. Such compounds and methods also have potential for the treatment of other conditions associated with dysregulated protein kinase
25 activity, such as inflammation and neoplastic disease.

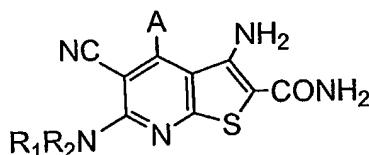
BRIEF DESCRIPTION OF THE INVENTION

The present invention comprises thienopyridine compounds of Formula I below, which are IKK β inhibitors with potential for use in treating HBV infection, and methods of treatment of HBV infection utilizing compounds of Formula I and other thienopyridines.

5

The present inventors have discovered that various thienopyridines are effective as IKK β inhibitors. Such compounds may be used for treatment of HBV, as well as other diseases that are directly or indirectly associated with a dysregulated kinase.

In one embodiment the present invention provides a compound of Formula I below



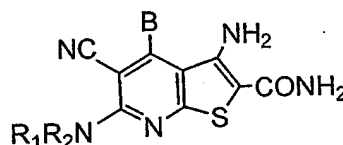
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Formula I

wherein A is a monocyclic or bicyclic aliphatic or aromatic group comprising 5 – 10 ring atoms, optionally containing 1 - 4 heteroatoms independently selected from O, N, and S, said aliphatic or aromatic group optionally substituted with 1-3 substituents independently selected from C₁–C₆ alkyl, C₁–C₆ alkoxy, C₁–C₆ alkenyl, C₁–C₆ alkenoxy, halo, cyano, hydroxy, trifluoromethyl, nitro, -S(O)_nR₃ where n = 0-2, -NR₄R₅, -NR₆C(O)R₇, -C(O)R₈, -COOR₉, -C(NH)R₁₀, and -CONR₁₁R₁₂; wherein R₁-R₁₂ are, independently, H, Ar₁NH-, C₁–C₆ alkyl, C₁–C₆ alkoxy, halo, cyano, hydroxy, trifluoromethyl, nitro, -S(O)_nR₁₃ where n = 0-2, -NR₁₄R₁₅, -NR₁₆C(O)R₁₇, -C(O)R₁₈, -COOR₁₉, -C(NH)R₂₀, Ar₂, or -C(NH)NR₂₁R₂₂, wherein R₁₃-R₂₂ are hydrogen, C₁–C₆ alkyl and C₁–C₆ alkenyl, and wherein R₁₃ may additionally be NH₂; and wherein all of said C₁–C₆ alkyl and said C₁–C₆ alkenyl substituents, all of the C₁–C₆ alkyl moieties of said C₁–C₆ alkoxy substituents, and all of the C₁–C₆ alkenyl moieties of said C₁–C₆ alkenoxy substituents are straight-chain, branched, or cyclic and are optionally substituted with 1-3 substituents selected independently from hydroxy, halo, cyano,

C₁-C₆ alkoxy, Ar₃, Ar₄CO₂-, C₁-C₆ alkyl-O-C(O)- and C₁-C₆ alkyl-NHCO- and Ar₅NHCO-; wherein Ar₁-Ar₅ are, independently, phenyl, naphthyl or pyridyl, optionally substituted with 1-3 substituents selected independently from hydroxy, halo, cyano, C₁-C₆ alkyl, and C₁-C₆ alkoxy, said C₁-C₆ alkyl, and C₁-C₆ alkoxy, all optionally substituted as provided above; or
 5 wherein R₁ and R₂ may, together with the nitrogen atom to which they are attached, form a five- or six-membered ring, optionally containing an additional ring heteroatom selected from oxygen and nitrogen, where said five- or six-membered ring may be optionally substituted as described for substituents R₁-R₉ above, and where said possible substituent Ar₂ may be fused to said five- or six-membered ring; or wherein R₁ may be 6,6-dimethyl-bicyclo[3.1.1]hept-2-yl-methyl; with provided that when R₁ and R₂ are both H, A is not unsubstituted thien-2-yl,
 10 and also provided that A is neither p-chlorophenyl nor p-bromophenyl.

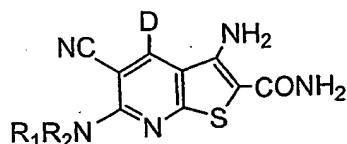
In another embodiment, the present invention provides a compound of Formula Ib in which R₁ and R₂ are as defined for Formula I and in which B is a group selected from the following: 1-propyl; dimethoxymethyl; 1-hydroxy-2-propyl; 1-methoxy-2-propyl;
 15 propen-2-yl; and 2-methylsulfanylethyl.



Formula Ib

In another embodiment, the present invention provides a method of treating HBV
 20 infection comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of Formula I.

In another embodiment, the present invention provides a method of treating HBV
 infection comprising administering to a patient in need of such treatment a therapeutically
 25 effective amount of a compound of Formula Ic



Formula Ic

in which R_1 and R_2 are as defined for Formula I and in which D is a C_1 - C_6 alkyl group, optionally substituted as described for C_1 - C_6 alkyl groups in Formula I

5

DETAILED DESCRIPTION OF THE INVENTION

The term "alkyl," as used herein, refers to a saturated straight-chain, branched or cyclic group of 1- 20 carbon atoms derived from an alkane by the removal of one hydrogen atom.

The term "alkenyl" as used herein refers to a monovalent straight or branched chain
10 group of 2-12 carbon atoms containing at least one carbon-carbon double bond derived from an alkene by the removal of one hydrogen atom.

The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular group through an oxygen atom.

The term "amino," as used herein, refers to a $-NR_aR_b$ group, where R_a and R_b are
15 independently selected from hydrogen, alkyl, aryl or heteroaryl.

The term "aminocarbonyl," as used herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein.

The term "aminocarbonyloxy," as used herein, refers to an aminocarbonyl group, as defined herein, appended to the parent molecular moiety through an oxy group, as defined
20 herein.

The term "aryl," as used herein, refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings. The aryl group can also be fused to a cyclohexane,

cyclohexene, cyclopentane or cyclopentene ring. The aryl groups of this invention can be optionally substituted.

The term "oxo," as used herein, refers to =O.

The term "carbonyl," as used herein, refers to a C=O group.

5 The term "cycloalkyl," as used herein, refers to a monovalent aliphatic cyclic hydrocarbon group of 3-12 carbons derived from a cycloalkane by the removal of a single hydrogen atom.

The terms "halo" or "halogen," as used herein, refer to F, Cl, Br, or I.

10 The term "heteroaryl" represents an aryl group containing in which one, two or three ring atoms are substituted with heteroatoms independently selected from nitrogen, oxygen, and sulfur.

The term "oxy," as used herein, refers to --O--.

The term "methylene," as used herein, refers to a --CH₂-- group.

15 The term "perfluoroalkyl," as used herein, refers to an alkyl group in which all of the hydrogen atoms have been replaced by fluoride atoms.

The term "phenyl," as used herein, refers to a monocyclic carbocyclic ring system having one aromatic ring. The aryl group can also be fused to a cyclohexane or cyclopentane ring. The phenyl groups of this invention can be optionally substituted.

20 The term "prodrug," as used herein, represents compounds which are transformed *in vivo* to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

25 The term "thioalkoxy," as used herein, refers to an alkyl group attached to the parent molecular group through a sulfur atom.

The term "treating," as used herein, refers to reversing, alleviating, or inhibiting the progress of the disease, disorder or condition, or one or more symptoms of such disease, disorder or condition, to which such term applies. Depending on the condition of the patient, as used herein, this term also refers to preventing a disease, disorder or condition, and includes preventing the onset of a disease, disorder or condition, or preventing the symptoms associated with a disease, disorder or condition. As used herein, this term also refers to reducing the severity of a disease, disorder or condition or symptoms associated with such disease, disorder or condition prior to affliction with the disease, disorder or condition. Such prevention or reduction of the severity of a disease, disorder or condition prior to affliction refers to administration of the composition of the present invention, as described herein, to a subject that is not at the time of administration afflicted with the disease, disorder or condition. "Preventing" also refers to preventing the recurrence of a disease, disorder or condition or of one or more symptoms associated with such disease, disorder or condition. The terms "treatment" and "therapeutically," as used herein, refer to the act of treating, as "treating" is defined above.

Synthetic Methods

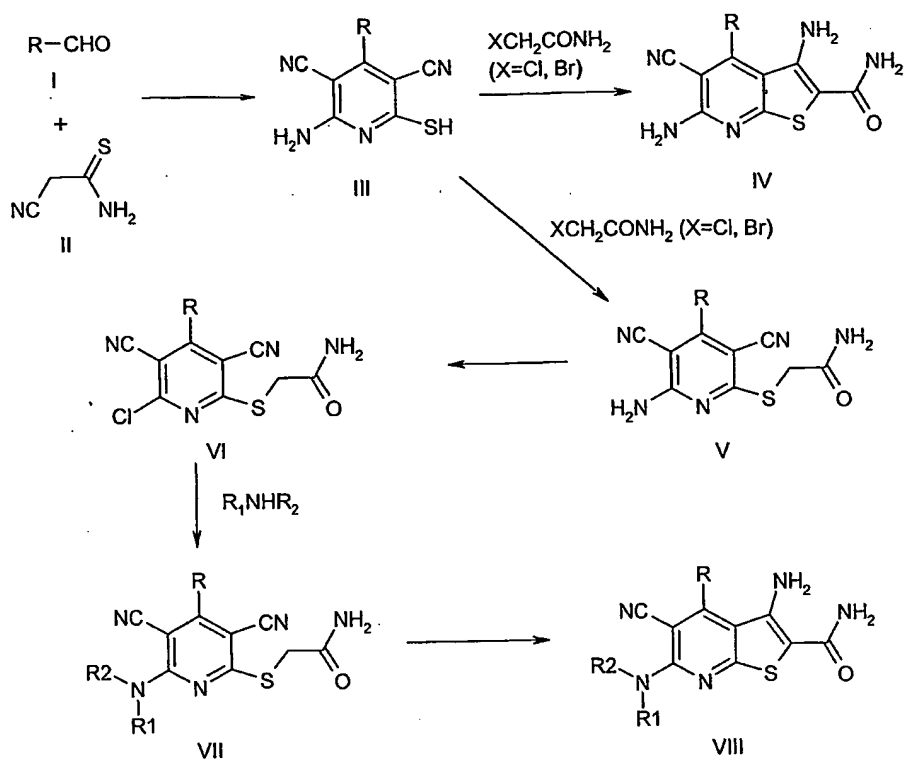
The compounds of this invention may be prepared by the general methods and examples presented below, and methods known to those of ordinary skill in the art. Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Reaction progress may be monitored by conventional methods such as thin layer chromatography (TLC) and mass spectrum (MS). Intermediates and products may be purified by methods known in the art, including column chromatography, HPLC or recrystallization.

Abbreviations which have been used in the descriptions of the schemes and the examples that follow are: n-BuLi for n-butyllithium, DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene, DMA for N,N-dimethylacetamide, DIBAL for diisobutylaluminum hydride, DME for dimethoxyethane, DMF for N,N-dimethylformamide, DMSO for dimethylsulfoxide, DIPEA for diisopropylethylamine, DPPA for diphenylphosphoryl azide, EDCI or EDC for 1-ethyl-3-

[3-(dimethylamino)propyl]-carbodiimide hydrochloride, Et₃N for triethylamine, Et₂O for diethyl ether, EtOAc for ethyl acetate, EtOH for ethanol, K₂CO₃ for potassium carbonate, LiAlH₄ for lithium aluminum hydride, LDA for lithium diisopropylamide, MeOH for methanol, NaOMe for sodium methoxide, NaOH for sodium hydroxide, HCl for hydrochloric acid, NMP for 1-methyl-2-pyrrolidinone, H₂/Pd for hydrogen and a palladium catalyst, iPrOH for isopropyl alcohol, PPh₃ for triphenylphosphine, THF for tetrahydrofuran, THP for tetrahydropyran, TFA for trifluoroacetic acid, and pyBOP for benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate.

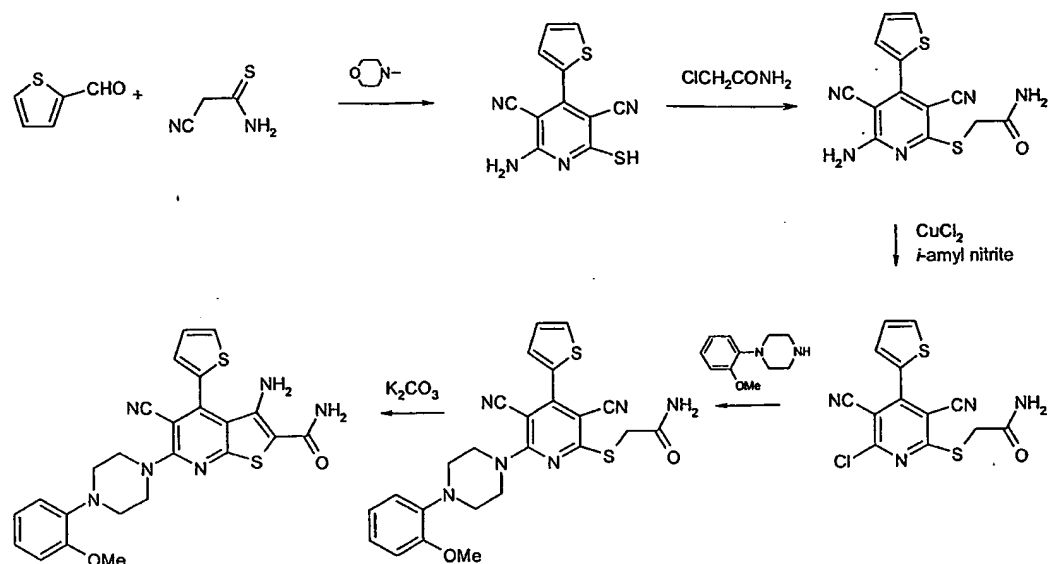
10 As illustrated in scheme 1, compounds of formula IV may be prepared starting with an aromatic or aliphatic aldehyde I. Reaction of I with cyanothioacetamide II in a suitable solvent such as ethanol, in the presence of a suitable base such as N-methylmorpholine, morpholine, triethylamine, provides the intermediates III. Reaction of III with chloro- or bromoacetamide in a suitable solvent such as ethanol, acetone, THF, in the presence of a
15 suitable base such as potassium carbonate, triethylamine, sodium ethoxide, with or without heating provides the desired compounds of formula IV. Also, reaction of III with chloro- or bromoacetamide in a suitable solvent such as acetone, in the presence of a suitable base such as triethylamine with milder condition comparing with formation of IV provides the non-cyclic intermediate V. Reaction of V with anhydrous copper chloride and i-amyl nitrite in
20 acetonitrile provides the 6-chloro intermediate VI. VI reacts with different amines in the presence of a suitable solvent such as ethanol to provide intermediates VII. Cyclization of VII in a suitable solvent such as ethanol, acetone, in the presence of a suitable base such as potassium carbonate provides the desired compounds of formula VIII.

25 **Scheme I**



SYNTHETIC EXAMPLES

- 5 **Example 1: Synthesis of 3-amino-5-cyano-6-[4-(2-methoxy-phenyl)-piperazin-1-yl]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (29)**



2-Amino-6-mercapto-4-thiophen-2-yl-pyridine-3,5-dicarbonitrile

A mixture of 2-thiophencarbaldehyde (5.61g, 0.05mol) and 2-cyanothioacetamide (10.01g, 0.1mol) in 100 ml of ethanol was added *N*-methylmorpholine (7.59g, 0.075mol) at room temperature. The resulting mixture was stirred at room temperature for 4 hours and then refluxed for 5 hours. The reaction mixture was cooled to room temperature and the resulting yellow crystals were filtered and washed with ethanol to give 8.8g (68%) of the desired product after drying *in vacuo*. ¹H-NMR (300MHz, DMSO-*d*₆): δ 7.86 (dd, *J*=0.9, 4.8Hz, 1H), 7.44 (dd, *J*=0.9, 3.6Hz, 1H), 7.21 (dd, *J*=3.6, 4.8Hz, 1H), 3.70 (brs, 2H), 2.93 (brs, 1H). ES MS *m/z* 259 (*M* + H)⁺, 257 (*M* - H)⁻.

2-(6-Amino-3,5-dicyano-4-thiophen-2-yl-pyridin-2-ylsulfanyl)-acetamide

A suspension of 2-amino-6-mercapto-4-thiophen-2-yl-pyridine-3,5-dicarbonitrile (7.74g, 0.03mol) and 2-chloroacetamide (2.82 g, 0.03 mol) in 150 ml of acetone was added triethylamine (3.03 g, 0.03 mol) with stirring at room temperature. The resulting mixture was stirred at room temperature for 5 hours and the precipitates was filtered and washed with acetone to give 9.3g (98%) of product as yellow crystals. ¹H-NMR (300 MHz, DMSO-*d*₆): δ 8.1 (brs, 2H), 7.94 (dd, *J*=1.2, 4.8Hz, 1H), 7.56 (dd, *J*=1.2, 3.6Hz, 1H), 7.49 (brs, 1H), 7.27 (dd, *J*=3.6, 4.8Hz, 1H), 7.26 (brs, 1H), 3.86 (s, 2H). ES MS *m/z* 316 (*M* + H)⁺, 314 (*M* - H)⁻.

2-(6-Chloro-3,5-dicyano-4-thiophen-2-yl-pyridin-2-ylsulfanyl)-acetamide

To a rapidly stirred mixture of anhydrous copper(II) chloride (1.9g, 14.1 mmol), i-amyl nitrite (2.4 ml, 17.9 mmol) in 200 ml of anhydrous acetonitrile was added 2-(6-amino-3,5-dicyano-4-thiophen-2-yl-pyridin-2-ylsulfanyl)-acetamide (3.7g, 11.8 mmol) under argon. The reaction mixture was heated at 65°C for 5 hours. After the mixture was cooled, the reaction solution was poured into 300 ml of 20% aqueous hydrochloric acid and extracted three times with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo*. The residue was recrystallized from ethanol to give 1.8g of yellow crystals (47%). ¹H-NMR (300MHz, DMSO-*d*₆): δ 8.08 (dd, J=1.2, 4.8Hz, 1H), 7.45 (brs, 1H), 7.72 (dd, J=1.2, 3.6Hz, 1H), 7.34 (brs, 1H), 7.34 (dd, J=3.6, 4.8Hz, 1H), 4.07 (s, 2H). ES MS *m/z* 335 (M + H)⁺, 333(M - H)⁻.

2-(6-[4-(2-methoxy-phenyl)-piperazin-1-yl]-3,5-dicyano-4-thiophen-2-yl-pyridin-2-ylsulfanyl)-acetamide

A mixture of 2-(6-chloro-3,5-dicyano-4-thiophen-2-yl-pyridin-2-ylsulfanyl)-acetamide (184mg, 0.55mmol) and 1-(2-methoxyphenyl)-piperazine (127mg, 0.66mmol) in 2 ml of ethanol was stirred for overnight at room temperature. The precipitates was filtered and washed with ethanol to give 170 mg (63%) of the desired product as white solid. ¹H-NMR (300MHz, DMSO-*d*₆): δ 7.97 (d, J=5.1Hz, 1H), 7.65 (brs, 1H), 7.61 (d, J=3.6Hz, 1H), 7.29 (dd, J=3.6, 5.1Hz, 1H), 7.29 (brs, 1H), 6.98-6.88 (m, 4H), 4.04 (m, 4H), 3.91 (s, 2H), 3.80 (s, 3H), 3.08 (m, 4H). ES MS *m/z* 491 (M + H)⁺, 489(M - H)⁻.

3-Amino-5-cyano-6-[4-(2-methoxy-phenyl)-piperazin-1-yl]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (29)

To a solution of 2-(6-[4-(2-methoxy-phenyl)-piperazin-1-yl]-3,5-dicyano-4-thiophen-2-yl-pyridin-2-ylsulfanyl)-acetamide (170mg, 0.35mmol) in 10 ml of 1:1 mixture of ethanol and acetone was added anhydrous potassium carbonate (97mg, 0.7mmol). The resulting mixture was heated to 65°C with stirring for 5 hours. The reaction mixture was filtered and washed with acetone. The filtrate was evaporated to dryness *in vacuo* and the residue was recrystallized from ethanol to give 130 mg (76%) of the desired product as yellow crystals. ¹H-NMR (300MHz, DMSO-*d*₆): δ 7.96 (d, J=5.1Hz, 1H), 7.40 (d, J=3.6Hz, 1H), 7.30 (dd, J=3.6,

5.1Hz, 1H), 7.17 (brs, 2H), 6.97-6.84 (m, 4H), 5.83 (brs, 2H), 3.79 (s, 3H), 3.78 (m, 4H), 3.11 (m, 4H). ES MS m/z 491 ($M + H$)⁺, 489($M - H$)⁻.

The following compounds were prepared using the same procedure described in Example 1, and substituting as appropriate a suitable aldehyde for 2-thiophencarbaldehyde as the starting material. In some cases, if the product was not re-crystallized from ethanol, the reaction mixture was purified by flash column or preparative HPLC.

3-Amino-5-cyano-6-(2-morpholin-4-yl-ethylamino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (30)

3-Amino-5-cyano-6-methylamino-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (31)

3-Amino-5-cyano-6-morpholin-4-yl-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (32)

3-Amino-5-cyano-6-[N'-(4-fluoro-phenyl)-hydrazino]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (33)

(S)-2-(3-Amino-2-carbamoyl-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridin-6-ylamino)-3-phenyl-propionic acid ethyl ester (34)

(S)-2-(3-Amino-2-carbamoyl-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridin-6-ylamino)-4-phenyl-butyric acid ethyl ester (35)

(S)-2-(3-Amino-2-carbamoyl-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridin-6-ylamino)-3-(1H-imidazol-4-yl)-propionic acid methyl ester (36)

(S)-2-(3-Amino-2-carbamoyl-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridin-6-ylamino)-4-methyl-pentanoic acid methyl ester (37)

3-Amino-5-cyano-6-(3,4-dihydro-1H-isoquinolin-2-yl)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (38)

3-Amino-5-cyano-6-[3-(2-methyl-piperidin-1-yl)-propylamino]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (39)

3-Amino-5-cyano-6-(2-hydroxy-2-phenyl-ethylamino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (40)

10 3-Amino-5-cyano-6-[2-(4-hydroxy-phenyl)-ethylamino]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (41)

4-(3-Amino-2-carbamoyl-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridin-6-ylamino)-piperidine-1-carboxylic acid ethyl ester (42)

15 3-Amino-5-cyano-6-[2-(1-methyl-pyrrolidin-2-yl)-ethylamino]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (43)

1-(3-Amino-2-carbamoyl-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridin-6-yl)-piperidine-4-carboxylic acid ethyl ester (44)

3-Amino-5-cyano-6-(3-imidazol-1-yl-propylamino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (45)

25 3-Amino-5-cyano-6-isopropylamino-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (46)

3-Amino-5-cyano-6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (47)

30 3-Amino-5-cyano-6-[(tetrahydro-furan-2-ylmethyl)-amino]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (48)

3-Amino-5-cyano-6-(3,3-dimethyl-butylamino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (49)

- 5 3-Amino-5-cyano-6-(((R)-6,6-dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-amino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (50)

3-Amino-6-(1-benzyl-piperidin-4-ylamino)-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (51)

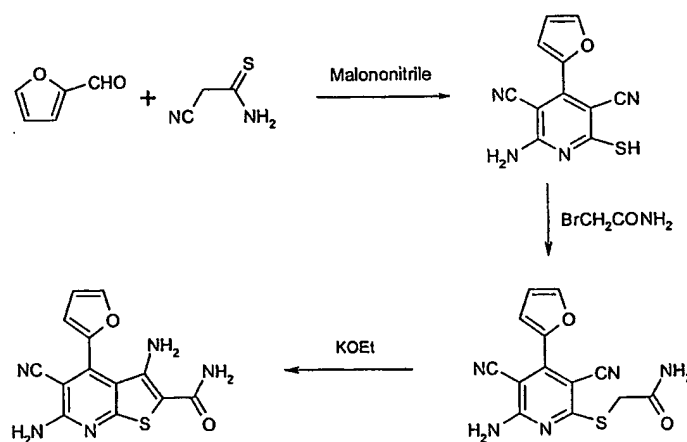
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3-Amino-6-(4-carbamoyl-piperidin-1-yl)-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (52)

- 15 3-Amino-5-cyano-6-(2-phenylamino-ethylamino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (53)

3-Amino-5-cyano-6-[(naphthalen-1-ylmethyl)-amino]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (54)

- 20 **Example 2: Synthesis of 3,6-diamino-5-cyano-4-furan-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (57)**



2-Amino-6-mercapto-4-furan-2-yl-pyridine-3,5-dicarbonitrile

Furan-2-carbaldehyde (0.96 g, 10 mmol), malononitrile (0.66 g, 10 mmol) and 2-cyanothioacetamide (1.0g, 10 mmol) were dissolved in EtOH (50ml). Piperidine (0.05 ml) was added and the mixture was stirred at 90° C for 16 h and then evaporated with silica gel. The mixture was purified on a silica gel column, eluted with hexane/EtOAc (2:1 → 1:2), to give a yellow powder (1.73 g, 67%).

2-(6-Amino-3,5-dicyano-4-furan-2-yl-pyridin-2-ylsulfanyl)-acetamide

The above product (258 mg, 1mmol) was dissolved in THF (10 ml), DMF (2 ml) and Et₃N (0.153 ml, 1.1 mmol) and treated with 2-bromoacetamide (152 mg, 1.1 mmol). The mixture was stirred at room temperature for 4 h followed by TLC and MS. The mixture was concentrated and water was added to the residue. After 1 h the solid was filtered and washed with water, then dried to give a yellow powder (214 mg, 68%).

3,6-Diamino-5-cyano-4-furan-2-yl-thieno[2,3-b]pyridine-2-carboxamide (57)

The above dry intermediate (315 mg, 1 mmol) was dissolved in EtOH (12 ml) and treated with KOEt (93 mg, mmol). The mixture was stirred at 80° C for 2 h followed by TLC. Silica gel was added to the mixture and the mixture was evaporated and purified on a silica gel column, eluted with hexane/EtOAc 1:1 to 0:1 to give a yellow powder (185 mg, 62%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 6.08 (s, 2H), 6.77 (s, 1H), 7.00 (s, 2H), 7.31 (s, 1H), 7.96 (s, 1H), 8.10 (s, 1H).

The following compounds were prepared using the similar procedure described in Example 2 and substituting a suitable aldehyde for 2-thiophencarbaldehyde as the starting material. In the case the product was not recrystallized from ethanol, the reaction mixture was purified by flash chromatography or preparative HPLC.

3-Amino-5-cyano-6-dimethylamino-4-isopropyl-thieno[2,3-b]pyridine-2-carboxylic acid amide (55)

3,6-Diamino-5-cyano-4-(1-methyl-1H-pyrrol-2-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide (56)

3,6-Diamino-5-cyano-4-(3-methyl-thiophen-2-yl)-thieno[2,3-b]pyridine-2-carboxylic acid
amide (58)

5 3,6-Diamino-5-cyano-4-(3H-imidazol-4-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide
(59)

3,6-Diamino-5-cyano-4-thiophen-3-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (60)

10 3,6-Diamino-5-cyano-4-(2-methylsulfanyl-ethyl)-thieno[2,3-b]pyridine-2-carboxylic acid
amide (63)

3,6-Diamino-5-cyano-4-(3,4-dihydroxy-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid
amide (64)

15 3,6-Diamino-4-benzyl-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide (65)

3,6-Diamino-5-cyano-4-(3,5-dimethoxy-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid
amide (66)

20 4-(3,6-Diamino-2-carbamoyl-5-cyano-thieno[2,3-b]pyridin-4-yl)-benzoic acid (67)

4-(3,6-Diamino-2-carbamoyl-5-cyano-thieno[2,3-b]pyridin-4-yl)-benzoic acid methyl ester
(68)

25 3,6-Diamino-4-(3-bromo-phenyl)-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide (69)

3,6-Diamino-5-cyano-4-pyridin-3-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (70)

30 3,6-Diamino-4-(3-fluoro-phenyl)-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide (71)

3,6-Diamino-4-(4-trifluoromethyl-phenyl)-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid

amide (72)

3,6-Diamino-5-cyano-4-pyridin-4-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (73)

5 3,6-Diamino-4-(4-cyano-phenyl)-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide (74)

3,6-Diamino-4-(4-fluoro-phenyl)-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide (75)

3,6-Diamino-5-cyano-4-furan-3-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (76)

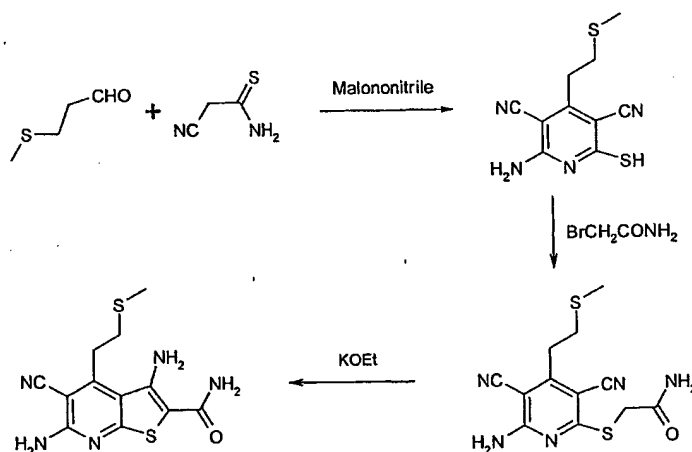
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3,6-Diamino-4-(4-chloro-phenyl)-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide (77)

3,6-Diamino-5-cyano-4-[3-(3-piperidin-1-yl-propionylamino)-phenyl]-thieno[2,3-b]pyridine-2-carboxylic acid amide (78)

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Example 3: Synthesis of 3,6-Diamino-5-cyano-4-(2-methylsulfanyl-ethyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide (63)



2-Amino-6-mercapto-4-(2-methylsulfanyl-ethyl)-pyridine-3,5-dicarbonitrile

20 3-Methylsulfanyl-propionaldehyde (1.04 g, 10 mmol), malononitrile (0.66 g, 10 mmol) and 2-cyanothioacetamide (1.0g, 10 mmol) were dissolved in EtOH (50ml). Piperidine (0.05 ml) was added and the mixture was stirred at 90° C for 16 h and then evaporated with silica gel.

The mixture was purified on a silica gel column, eluted with hexane/EtOAc (2:1 → 1:2), to give a yellow powder (1.80 g, 72%).

2-[6-Amino-3,5-dicyano-4-(2-methylsulfanyl-ethyl)-pyridin-2-ylsulfanyl]-acetamide

The above product (250 mg, 1 mmol) was dissolved in THF (10 ml), DMF (2 ml) and Et₃N (0.153 ml, 1.1 mmol) and treated with 2-bromoacetamide (152 mg, 1.1 mmol). The mixture was stirred at room temperature for 4 h monitored by TLC and MS. The mixture was concentrated and water was added to the residue. After 1 h the solid was filtered and washed with water, then dried to give a yellow powder (249 mg, 81%).

3,6-Diamino-5-cyano-4-(2-methylsulfanyl-ethyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide (63)

The above dry intermediate (307 mg, 1 mmol) was dissolved in EtOH (12 ml) and treated with KOEt (93 mg, mmol). The mixture was stirred at 80° C for 2 h monitored by TLC. Silica gel was added to the mixture and the mixture was evaporated and purified on a silica gel column, eluted with hexane/EtOAc 1:1 to 0:1 to give a yellow powder (206 mg, 67%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.10 (s, 3H), 2.82 (t, 2H), 3.36 (t, 2H), 6.84 (s, 2H), 7.10 (s, 2H), 7.23 (s, 2H).

The following compounds were prepared by using the same procedure described in Example 3 and substituting a suitable aldehyde for 3-methylsulfanyl-propionaldehyde as the starting material. In the case the product was not recrystallized from ethanol, the reaction mixture was purified by flash chromatography or preparative HPLC.

3,6-Diamino-5-cyano-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide (61)

3,6-Diamino-5-cyano-4-dimethoxymethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide (62)

Preferred Uses of Contemplated Compounds and Compositions

Based on the unexpected discovery that numerous protein kinase inhibitors may be employed as antiviral agents, the inventors generally contemplate that known and novel kinase inhibitors may be used as antiviral drugs and *vice versa* – antiviral drugs as kinase inhibitors (*e.g.*, in the treatment of diseases known to be associated with dysregulation of kinases, especially including neoplastic diseases). Thus, in one general aspect of the inventive subject matter, all known kinase inhibitors, and particularly those contemplated herein and/or involved in a signaling cascade may be employed as antiviral agents (and *vice versa*).

For example, various contemplated compounds exhibit IKK β inhibitory activity and have been demonstrated by the inventors to be effective anti-HBV agents. However, it should be recognized that numerous other kinase inhibitors may also demonstrate an antiviral effect against a variety of viruses other than HBV, and especially contemplated alternative viruses include those in which the virus directly or indirectly interferes with the host cell's signal transduction, and/or in which the viral infection is associated with an inflammatory response of the host (*e.g.*, HCV). Still further, it should be recognized that contemplated anti-HBV compounds may also be used as therapeutic agents against diseases associated with IKK β dysregulation which may include, melanoma, mammary carcinoma, non-small cell lung carcinoma, colorectal carcinoma, squamous-cell carcinoma, leukemia, lymphoma, thyroid carcinoma, fibrosarcoma, pancreatic cancer, prostate cancer, multiple myeloma, ovarian cancer, rheumatoid arthritis, multiple sclerosis, psoriasis, or inflammatory disorders.

Therefore, the inventors especially contemplate pharmaceutical compositions in which contemplated kinase inhibitory compounds are present at a concentration effective to inhibit or reduce viral propagation in a patient's cell. The term "viral propagation" as used herein especially includes reduction of viral replication, synthesis, processing and/or assembly of viral polypeptides, viral entry into the host cell, and release of viral particles from an infected cell.

Contemplated Pharmaceutical Compositions

It is particularly preferred that contemplated compounds are included in a pharmaceutical composition that is formulated with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray. The term "parenteral" administration as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intra-articular injection and infusion.

Pharmaceutical compositions for parenteral injection preferably comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

Contemplated compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active compounds may also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes may be used. The present compositions in liposome form may contain, in addition to a compound of the present invention, stabilizers,

preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

5 The compounds of the present invention may be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. By "pharmaceutically acceptable salt" is meant those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio.

10 Pharmaceutically acceptable salts are well-known in the art. For example, S. M. Berge, et al. describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66: 1 et seq. The salts may be prepared in situ during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable acid. Representative acid addition salts include, but are not limited to acetate, adipate, alginate,

15 citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate,

20 thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and

25 phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

30 Basic addition salts can be prepared in situ during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a

suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like. Preferred salts of the compounds of the invention include phosphate, TRIS, and acetate.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. Generally, dosage levels of about 1 to about 500, more preferably of about 5 to about 50 mg of an active compound per kilogram of body weight per day are administered orally to a mammalian patient. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, *e.g.*, two to four separate doses per day.

Examples

The following examples are provided to illustrate the inhibition of IKK β and HBV replication independently using compounds in the invention. However, it should be appreciated that numerous modifications of the compounds, assay and/or virus may result in similarly beneficial results. Consequently, the examples below are given only to provide exemplary guidance to a practitioner.

IKK β Cell-based Assay

A cell-based assay screening system using an NF κ B-Luc cell line was designed to study IKK β activity. The parental cell line of NF κ B-Luc is the 293 human embryonic kidney cell line, which was transfected to express the firefly luciferase gene under the control of an NF κ B responsive element. Treatment of NF κ B-Luc cells with tumor necrosis alpha (TNF α) induces activation of IKK β , leading to phosphorylation, ubiquitination and degradation of I κ B, and the subsequent translocation of NF κ B to the nucleus. Nuclear translocation of NF κ B results in its ability to initiate gene transcription, which can be detected by the luciferase reporter system. Therefore, in this system, inhibition of IKK β enzymatic activity is expected to result in inhibition of luciferase activity. For compound testing, 7500 NF κ B-Luc cells were added per well of 384-well plates and incubated for 16 hours at 37°C in a humidified incubator with 5% CO₂. Cells were pre-incubated with various concentrations of compound diluted in MEM/10% FBS. After one hour, cells were treated with 20 ng/mL TNF α diluted in MEM/10% FBS. After a 4.5-hour incubation, cells were lysed and luciferase activity was measured. IKK β inhibitory activity was calculated based on reduction of the luciferase signal and expressed as EC₅₀ (effective concentration to reduce the luciferase signal by 50%).

IKK β In Vitro Assay

For determination of IC₅₀ values, an *in vitro* IKK β assay was designed to study IKK β enzymatic activity in a cell-free system. His-tagged human IKK β expressed from a baculovirus construct in Sf9 insect cells and Glutathione S Transferase (GST)-I κ B α fusion protein (I κ B α residues 1 through 54) expressed in *E. coli* were purified and utilized in an *in vitro* radiolabel incorporation assay. The reaction contained 25 mM HEPES, pH7.4, 50 mM NaCl, 1 mM MgCl₂, 0.2 mM EDTA and 2.5 mM DTT. Purified IKK β (100 nM) was pre-incubated with compound for 30 minutes at room temperature. The kinase reaction was initiated by adding 5 μ M GST-I κ B α substrate, 1 μ M unlabeled ATP and 0.5 μ Ci ³³P- γ -ATP. The reaction was allowed to proceed at room temperature for 60 minutes and terminated by the addition 100 μ l 1% trichloroacetic acid (TCA). The reaction was transferred to a 96-well glass fiber filter plate previously blocked with 1% pyrophosphate. The filter plate was washed five times with water and twice with absolute ethanol and dried. Liquid scintillation cocktail was added to each well and radiolabel incorporation was quantified using the Packard TopCount HTS Scintillation Counter. Inhibition of IKK β activity was calculated based on

reduction of the radioactive signal and reported as IC₅₀ (inhibitory concentration to reduce the signal by 50%).

HBV Screening Assay

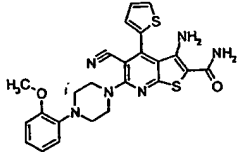
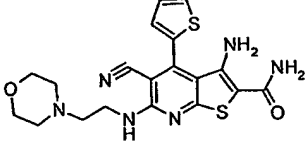
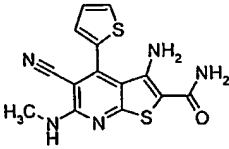
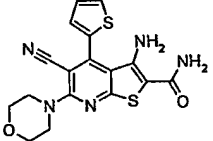
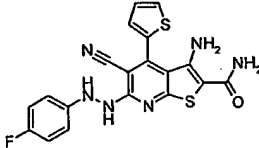
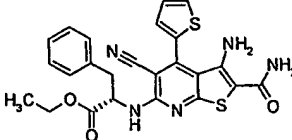
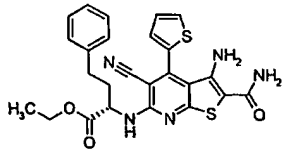
HepG2 cells were transduced using a baculovirus to deliver the HBV genome essentially as previously described (Delaney et al. in *Hepatology* 1998; 28: 1134-1146). Transduced cells were cultured in supplemented EMEM media with 10% fetal bovine serum in a 5% CO₂ incubator at 37°C for three days in the presence of test compounds. The cells were lysed in a buffer containing 0.5% NP-40 and 500 mg/ml proteinase K. A solid-phase hybridization was performed to capture the viral DNA and to label the target DNA with Digoxigenin-labeled DNA probes. The viral DNA was detected by ELISA using horseradish peroxidase-conjugated anti-digoxigenin antibodies.

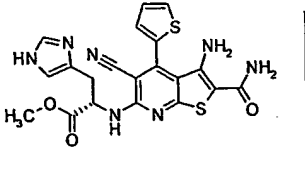
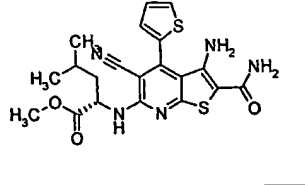
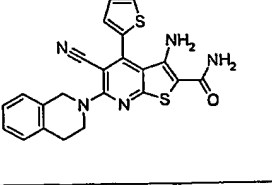
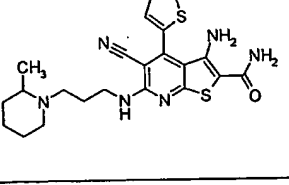
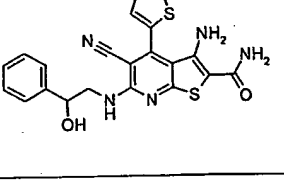
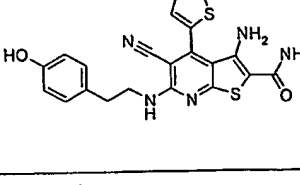
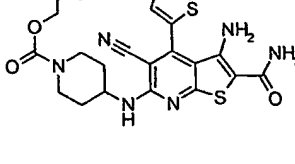
The EC₅₀ values were determined using ExcelFit software from the inhibition values of a titration curve for each compound. For CC₅₀ determinations, the same titration of compounds was co-cultured with non-transduced HepG2 for three days under the conditions described above. The Promega CellTiter 96 Aqueous One Solution Cell Proliferation Assay was used to measure cell proliferation/viability. The CC₅₀ values were determined using ExcelFit software from the inhibition values of the titration curve for each compound.

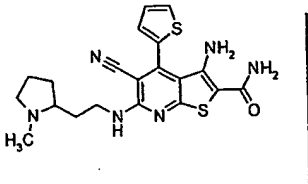
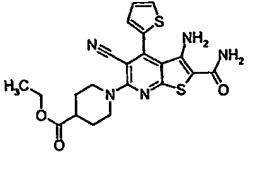
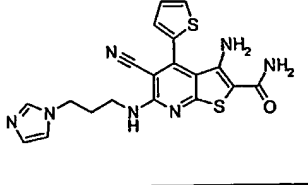
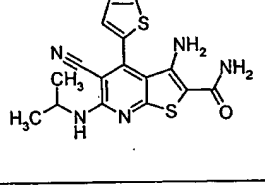
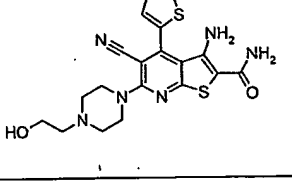
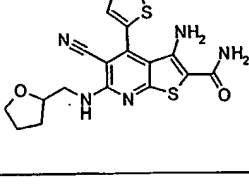
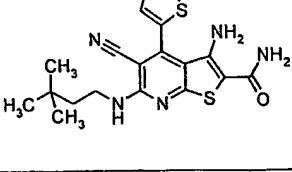
Test Results for Selected Contemplated Compounds

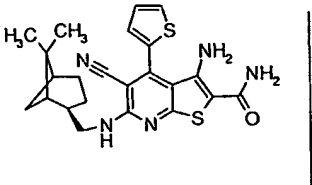
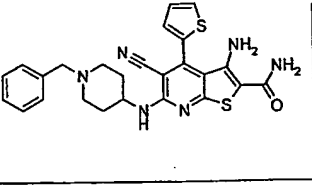
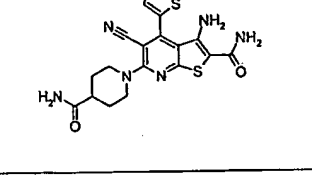
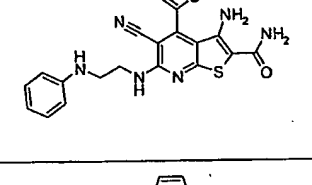
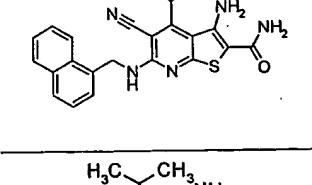
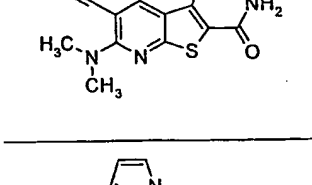
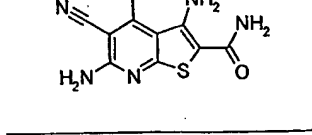
Table 1 below lists selected compounds with their structures and corresponding antiviral activity (EC₅₀ in μ M) and IKK β inhibitory activity (EC₅₀ and IC₅₀ in μ M). Antiviral activity and IKK β inhibitory activity was determined using assay systems as described above. All tested compounds had a CC₅₀ value of greater than 50.000 μ M. ND means not determined. (A: <1 μ M, B: 1-10 μ M, C: >10 μ M)

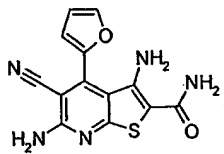
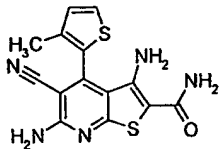
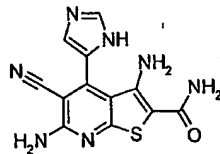
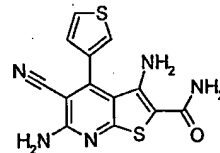
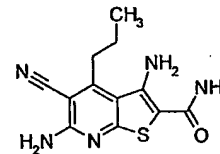
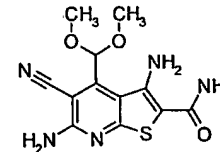
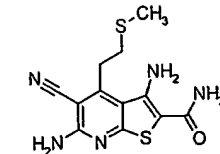
No	Name	Structure	IKK2 IC ₅₀	IKK2 EC ₅₀	HBV EC ₅₀
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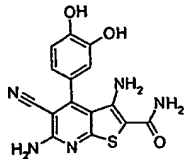
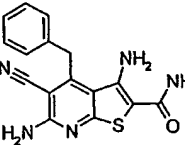
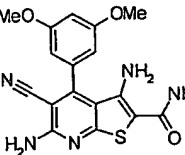
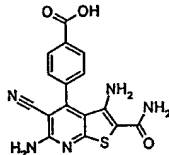
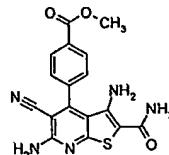
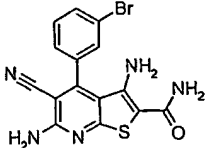
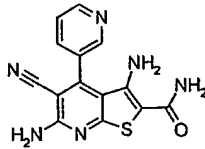
29	3-Amino-5-cyano-6-[4-(2-methoxy-phenyl)-piperazin-1-yl]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	B	B
30	3-Amino-5-cyano-6-(2-morpholin-4-yl-ethylamino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	C
31	3-Amino-5-cyano-6-methylamino-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	B	A
32	3-Amino-5-cyano-6-morpholin-4-yl-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	C	C
33	3-Amino-5-cyano-6-[N'-(4-fluoro-phenyl)-hydrazino]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	B	C
34	(S)-2-(3-Amino-2-carbamoyl-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridin-6-ylamino)-3-phenyl-propionic acid ethyl ester		C	B	ND
35	(S)-2-(3-Amino-2-carbamoyl-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridin-6-ylamino)-4-phenyl-butyric acid ethyl ester		B	C	C

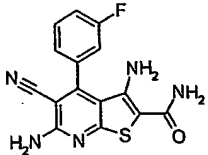
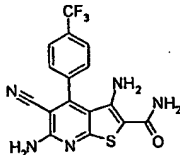
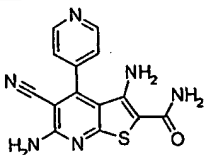
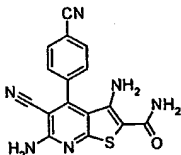
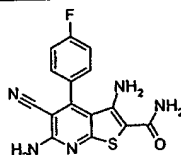
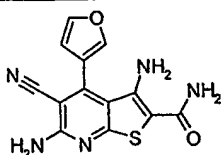
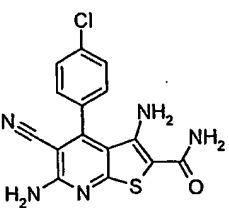
36	(S)-2-(3-Amino-2-carbamoyl-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridin-6-ylamino)-3-(1H-imidazol-4-yl)-propionic acid methyl ester		C	C	C
37	(S)-2-(3-Amino-2-carbamoyl-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridin-6-ylamino)-4-methyl-pentanoic acid methyl ester		B	C	C
38	3-Amino-5-cyano-6-(3,4-dihydro-1H-isoquinolin-2-yl)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	C	C
39	3-Amino-5-cyano-6-[3-(2-methyl-piperidin-1-yl)-propylamino]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	C
40	3-Amino-5-cyano-6-(2-hydroxy-2-phenyl-ethylamino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	C	C
41	3-Amino-5-cyano-6-[2-(4-hydroxy-phenyl)-ethylamino]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	C	C
42	4-(3-Amino-2-carbamoyl-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridin-6-ylamino)-piperidine-1-carboxylic acid ethyl ester		C	C	C

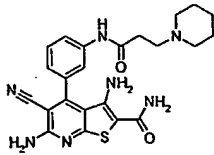
43	3-Amino-5-cyano-6-[2-(1-methyl-pyrrolidin-2-yl)-ethylamino]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	C
44	1-(3-Amino-2-carbamoyl-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridin-6-yl)-piperidine-4-carboxylic acid ethyl ester		B	C	C
45	3-Amino-5-cyano-6-(3-imidazol-1-yl-propylamino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	C	C
46	3-Amino-5-cyano-6-isopropylamino-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	C	C
47	3-Amino-5-cyano-6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	C	C
48	3-Amino-5-cyano-6-[(tetrahydro-furan-2-ylmethyl)-amino]-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	C	C
49	3-Amino-5-cyano-6-(3,3-dimethyl-butylamino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	C

50	3-Amino-5-cyano-6-(((R)-6,6-dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-amino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	B
51	3-Amino-6-(1-benzyl-piperidin-4-ylamino)-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	C	C
52	3-Amino-6-(4-carbamoyl-piperidin-1-yl)-5-cyano-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	C	C
53	3-Amino-5-cyano-6-(2-phenylamino-ethylamino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	C
54	3-Amino-5-cyano-6-((naphthalen-1-ylmethyl)-amino)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	C
55	3-Amino-5-cyano-6-dimethylamino-4-isopropyl-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	C
56	3,6-Diamino-5-cyano-4-(1-methyl-1H-pyrrol-2-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	B	A

57	3,6-Diamino-5-cyano-4-furan-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	B
58	3,6-Diamino-5-cyano-4-(3-methyl-thiophen-2-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	B	A
59	3,6-Diamino-5-cyano-4-(3H-imidazol-4-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	C
60	3,6-Diamino-5-cyano-4-thiophen-3-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	B	A
61	3,6-Diamino-5-cyano-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	B	C
62	3,6-Diamino-5-cyano-4-dimethoxymethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	B
63	3,6-Diamino-5-cyano-4-(2-methylsulfanyl-ethyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	B	B

64	3,6-Diamino-5-cyano-4-(3,4-dihydroxy-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	C
65	3,6-Diamino-4-benzyl-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	C
66	3,6-Diamino-5-cyano-4-(3,5-dimethoxy-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	C
67	4-(3,6-Diamino-2-carbamoyl-5-cyano-thieno[2,3-b]pyridin-4-yl)-benzoic acid		C	ND	C
68	4-(3,6-Diamino-2-carbamoyl-5-cyano-thieno[2,3-b]pyridin-4-yl)-benzoic acid methyl ester		B	ND	C
69	3,6-Diamino-4-(3-bromo-phenyl)-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide		ND	ND	A
70	3,6-Diamino-5-cyano-4-pyridin-3-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		A	ND	ND

71	3,6-Diamino-4-(3-fluoro-phenyl)-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	ND	ND
72	3,6-Diamino-4-(4-trifluoromethyl-phenyl)-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	ND
73	3,6-Diamino-5-cyano-4-pyridin-4-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	C	ND
74	3,6-Diamino-4-(4-cyano-phenyl)-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	B	ND
75	3,6-Diamino-4-(4-fluoro-phenyl)-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide		C	A	ND
76	3,6-Diamino-5-cyano-4-furan-3-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	B	A
77	3,6-Diamino-4-(4-chloro-phenyl)-5-cyano-thieno[2,3-b]pyridine-2-carboxylic acid amide		B	B	A

78	3,6-Diamino-5-cyano-4-[3-(3-piperidin-1-yl-propionylamino)-phenyl]-thieno[2,3-b]pyridine-2-carboxylic acid amide		ND	ND	ND
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Thus, specific embodiments and applications of protein kinase inhibitors have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted

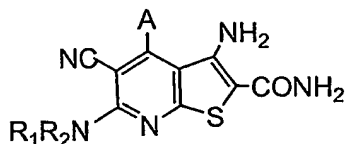
5 except in the spirit of the disclosure. Moreover, in interpreting the specification, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced

10 elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

CLAIMS

We claim

1. A compound according to Formula I below,



Formula I

wherein A is a monocyclic or bicyclic aliphatic or aromatic group comprising 5 – 10 ring
atoms, optionally containing 1 - 4 heteroatoms independently selected from O, N, and S, said
aliphatic or aromatic group optionally substituted with 1-3 substituents independently
selected from C₁–C₆ alkyl, C₁–C₆ alkoxy, C₁–C₆ alkenyl, C₁–C₆ alkenoxy, halo, cyano,
hydroxy, trifluoromethyl, nitro, -S(O)_nR₃ where n = 0-2, -NR₄R₅, -NR₆C(O)R₇, -C(O)R₈, -
COOR₉, -C(NH)R₁₀, and -CONR₁₁R₁₂;

wherein R₁-R₁₂ are, independently, H, Ar₁NH-, C₁–C₆ alkyl, C₁–C₆ alkoxy, halo, cyano,
hydroxy, trifluoromethyl, nitro, -S(O)_nR₁₃ where n = 0-2, -NR₁₄R₁₅, -NR₁₆C(O)R₁₇, -
C(O)R₁₈, -COOR₁₉, -C(NH)R₂₀, Ar₂, or -C(NH)NR₂₁R₂₂, wherein R₁₃-R₂₂ are hydrogen, C₁–
C₆ alkyl and C₁–C₆ alkenyl, and wherein R₁₃ may additionally be NH₂;

or wherein R₁ and R₂ may, together with the nitrogen atom to which they are attached, form a
five- or six-membered ring, optionally containing an additional ring heteroatom selected from
oxygen and nitrogen, where said five- or six-membered ring may be optionally substituted as
described for substituents R₁-R₉ above, and where said possible substituent Ar₂ may be fused
to said five- or six-membered ring;

or wherein R₁ may be 6,6-dimethyl-bicyclo[3.1.1]hept-2-yl-methyl;

and wherein all of said C₁–C₆ alkyl and said C₁–C₆ alkenyl substituents, all of the C₁–C₆ alkyl
moieties of said C₁–C₆ alkoxy substituents, and all of the C₁–C₆ alkenyl moieties of said C₁–

C₆ alkenoxy substituents are straight-chain, branched, or cyclic and are optionally substituted with 1-3 substituents selected independently from hydroxy, halo, cyano, C₁-C₆ alkoxy, Ar₃, Ar₄CO₂-, C₁-C₆ alkyl-O-C(O)- and C₁-C₆ alkyl-NHCO- and Ar₅NHCO-;

- 5 wherein Ar₁-Ar₅ are, independently, phenyl, naphthyl or pyridyl, optionally substituted with 1-3 substituents selected independently from hydroxy, halo, cyano, C₁-C₆ alkyl, and C₁-C₆ alkoxy, said C₁-C₆ alkyl, and C₁-C₆ alkoxy, all optionally substituted as provided above;

provided that when R₁ and R₂ are both H, A is not unsubstituted thien-2-yl,

10

and provided that A is neither *p*-chlorophenyl nor *p*-bromophenyl.

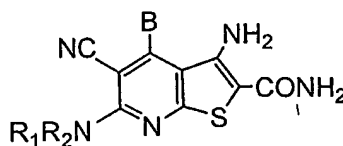
- 15 2. A compound according to claim 1, wherein A is an aromatic group comprising 5 – 10 ring atoms, optionally containing 1 – 4 heteroatoms independently selected from O, N, or S and optionally substituted as stated in claim 1.

- 20 3. A compound according to claim 1 wherein A is thien-2-yl, optionally substituted with C₁-C₆ alkyl, and R₁ and R₂ are, independently, hydrogen or methyl.

4. A compound according to claim 1 wherein A is thien-3-yl, optionally substituted with C₁-C₆ alkyl, and R₁ and R₂ are, independently, hydrogen or methyl.

- 25 5. A compound according to claim 3 wherein A is 3-methyl-thien-2-yl, optionally substituted as stated in claim 1, and R₁ and R₂ are, independently, hydrogen or methyl.

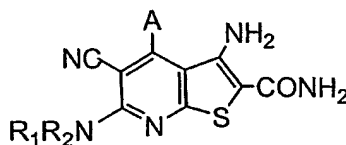
6. A compound according to claim 1 wherein A is phenyl, mono-substituted with halo, trifluoromethyl, or cyano, and R₁ and R₂ are, independently, hydrogen or methyl.
7. A compound according to claim 1 wherein A is pyrrolyl, optionally substituted as stated in claim 1, and R₁ and R₂ are, independently, hydrogen or methyl.
8. A compound according to claim 1 wherein A is furyl, optionally substituted as stated in claim 1, and R₁ and R₂ are, independently, hydrogen or methyl.
9. A compound according to claim 1 wherein A is pyridyl, optionally substituted as stated in claim 1, and R₁ and R₂ are, independently, hydrogen or methyl.
10. A compound of Formula Ib in which R₁ and R₂ are as defined for Formula I and in which B is selected from the following: 1-propyl; dimethoxymethyl; 1-hydroxy-2-propyl; 1-methoxy-2-propyl; propen-2-yl; and 2-methylsulfanylethyl.



Formula Ib

11. A method of treating hepatitis B virus comprising administering to a patient afflicted with hepatitis B virus a composition comprising a

pharmaceutically effective amount of a compound of Formula Ia, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically effective carrier,



Formula Ia

wherein A is a monocyclic or bicyclic aliphatic or aromatic group comprising 5 – 10 ring atoms, optionally containing 1 - 4 heteroatoms independently selected from O, N, and S, said aliphatic or aromatic group optionally substituted with 1-3 substituents independently
 10 selected from C₁–C₆ alkyl, C₁–C₆ alkoxy, C₁–C₆ alkenyl, C₁–C₆ alkenoxy, halo, cyano, hydroxy, trifluoromethyl, nitro, -S(O)_nR₃ where n = 0-2, -NR₄R₅, -NR₆C(O)R₇, -C(O)R₈, -COOR₉, -C(NH)R₁₀, and -CONR₁₁R₁₂;

wherein R₁-R₁₂ are, independently, H, Ar₁NH-, C₁–C₆ alkyl, C₁–C₆ alkoxy, halo, cyano,
 15 hydroxy, trifluoromethyl, nitro, -S(O)_nR₁₃ where n = 0-2, -NR₁₄R₁₅, -NR₁₆C(O)R₁₇, -C(O)R₁₈, -COOR₁₉, -C(NH)R₂₀, Ar₂, or -C(NH)NR₂₁R₂₂, wherein R₁₃-R₂₂ are hydrogen, C₁–C₆ alkyl and C₁–C₆ alkenyl, and wherein R₁₃ may additionally be NH₂;

or wherein R₁ and R₂ may, together with the nitrogen atom to which they are attached, form a
 20 five- or six-membered ring, optionally containing an additional ring heteroatom selected from oxygen and nitrogen, where said five- or six-membered ring may be optionally substituted as described for substituents R₁-R₉ above, and where said possible substituent Ar₂ may be fused to said five- or six-membered ring;

25 or wherein R₁ may be 6,6-dimethyl-bicyclo[3.1.1]hept-2-yl-methyl;

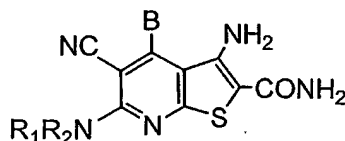
and wherein all of said C₁–C₆ alkyl and said C₁–C₆ alkenyl substituents, all of the C₁–C₆ alkyl moieties of said C₁–C₆ alkoxy substituents, and all of the C₁–C₆ alkenyl moieties of said C₁–

C₆ alkenoxy substituents are straight-chain, branched, or cyclic and are optionally substituted with 1-3 substituents selected independently from hydroxy, halo, cyano, C₁-C₆ alkoxy, Ar₃, Ar₄CO₂⁻, C₁-C₆ alkyl-O-C(O)- and C₁-C₆ alkyl-NHCO- and Ar₅NHCO-;

- 5 wherein Ar₁-Ar₅ are, independently, phenyl, naphthyl or pyridyl, optionally substituted with 1-3 substituents selected independently from hydroxy, halo, cyano, C₁-C₆ alkyl, and C₁-C₆ alkoxy, said C₁-C₆ alkyl, and C₁-C₆ alkoxy, all optionally substituted as provided above.

- 10 12. A method of treating hepatitis B virus comprising

administering to a patient afflicted with hepatitis B virus a composition comprising a pharmaceutically effective amount of a compound of Formula Ib, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically effective carrier,



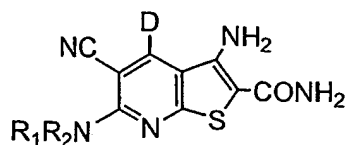
Formula Ib

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wherein B is selected from the following: 1-propyl; dimethoxymethyl; 1-hydroxy-2-propyl; 1-methoxy-2-propyl; propen-2-yl; and 2-methylsulfanylethyl.

13. A method of treating hepatitis B virus comprising administering to a patient afflicted with
 20 hepatitis B virus a composition comprising a pharmaceutically effective amount of a compound of Formula Ic, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically effective carrier,

Formula Ic



- wherein D is an acyclic C₁-C₆ alkyl group, optionally substituted with 1-3 substituents selected independently from hydroxy, halo, cyano, C₁-C₆ alkoxy, C₁-thioalkoxy, and Ar, wherein R₁ and R₂ are as defined in Claim 1, and Ar is a 5- or 6-membered aromatic ring, optionally containing 1 or 2 heteroatoms independently selected from O, N, and S and optionally substituted with 1-3 substituents selected, independently from halo, cyano, hydroxy and C₁-C₆ alkoxy.

14. A method according to claim 13, wherein D is an unsubstituted C₁-C₆ alkyl group.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/41632

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/4365; C07D 495/04; A61P 31/12
 US CL : 514/301; 546/114

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 U.S. : 514/301; 546/114

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Databsse CAPLUS on STN, AN 2001: 643807, ABBAS et al. 'Versatile starting materials for novel 1, w-bis(pyridin-4-ylphenoxy)alkanes, and their corresponding bis (thieno[2,3-b]pyridin-4-ylphenoxy) derivatives,' abstract, Journal of Chemical Research, Synopses, (2002), (4), 124-126, see entire abstract.	1, 2
A	Database CAPLUS on STN, AN 2000:307588, HUSSEIN et al. 'Polycyclic pyridines: synthesis of pyridothienopyrimidines pyridothienotriazines and pyridothienotriazepines,' Phosphorus, Sulfur and Silicon and the Related Elements (2002), 159, 55-68, see entire abstract.	1-14
X	Database CHEMCATS on STN, AN 2003:2404176, abstract, Interbioscreen Compound Library Catalog, 09 may 2003 (09.05.2003), see entire abstract.	1, 2
X	Database CHEMCATS on STN, AN 2001:2498902, abstract, Interbioscreen Compound Library Catalog, 09 May 2003 (09.05.2003), see entire abstract.	1, 2
X	Database CHEMCATS on STN, AN 2003:2192314, abstract, ChemDiv, Inc. Product Library Catalog, 25 April 2003 (25.04.2003), see entire abstract.	1, 2



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	
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"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search

14 April 2005 (14.04.2005)

Date of mailing of the international search report

12 MAY 2005

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
 Commissioner for Patents
 P.O. Box 1450
 Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Evelyn Huang
 Telephone No. 703-308-1235